REMARKS

Prior to this amendment, claims 1-6, 10 and 13-22 have been canceled without prejudice. Claims 7 - 9, 11, 12, 23-35 are pending. In this Amendment, claims 7 -22, 24 – 26 and 28 – 35 have been canceled without prejudice. Claims 23 has been amended. Support for these amendments can be found in the specification on page 63, line 6 to page 64, line 2, Reference Examples 1 and 2, and Examples 5, 6 and 12. No new matter has been added by this amendment.

Applicants respectfully reserve the right to pursue any non-elected, canceled or otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications.

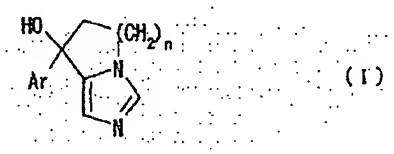
It is submitted that the claims, herewith and as originally presented were in full compliance with the requirements of 35 U.S.C. § 112. The amendment of the claims, as presented herein, is not made for purposes of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112. Rather, this amendment is made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendment should not give rise to any estoppel.

Reconsideration and withdrawal of the rejections of this application in view of the amendments and remarks herewith, is respectfully requested, as the application is in condition for allowance.

1. Claims 23 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tasaka et al. (WO 02/40484) in view of Mazer et al. (US 5,160,742).

> The claimed invention is a controlled release composition for oral administration, wherein (A) a core containing (1) (+)-6-(7-hydroxy-6, 7-dihydro- 5H-pyrrolo [1,2-c] imidazol-7-yl)-N-methyl-2-naphthamide or a salt thereof, and (2) a hydrophilic polymer selected from hydroxypropylcellulose and low-substituted hydroxypropylcellulose, which is coated with (B) a coating layer containing (1) methacrylic acid copolymers as an enteric coating

agent, (2) talc as a lubricant, and (3) a plasticizer selected from polyethylene glycol and triethyl citrate, wherein the core is in a granule form having the average particle diameter of from about 50 to about 2000 μm.
Tasaka teaches a compound of the formula:



wherein n is an integer of 1 to 3; and Ar is an optionally substituted aromatic ring, or a salt thereof (Page 4, lines 1-8). The compound (+)-6-(7-hydroxy- 6, 7-dihydro- 5H- pyrrolo [1,2-c] imidazol-7-yl)-N-methyl-2-naphthamide is disclosed as one of the compounds (Page 6, lines 24-25). A pharmaceutical composition containing the compound, which is an antitumor agent, and which is an agent for the prophylaxis or treatment of breast cancer or prostate cancer is disclosed (Page 8, lines 6-14). Pharmaceutically acceptable carriers that are used in the composition, including an excipient, a lubricant, a binder, a disintegrating agent and a thickener are disclosed (Page 39, lines 29-33). "Preferable examples of the excipient include lactose, sucrose, D-mannitol, starch, ... Preferable examples of the lubricant include magnesium stearate, calcium stearate, talc, colloidal silica ... Preferable examples of the binder include ... hydroxypropylcellulose, hydroxypropylmethylcellulose ... Preferable examples of the disintegrating agent include starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, crosscarmellose sodium, sodium carboxymethyl starch ... Preferable examples of the thickener include natural gums ... Preferable examples of the solvent include ... propylene glycol ... Preferable examples of the dispersing agent include polyethylene glycol ... Preferable examples of the solubilizer include polyethylene glycol, propylene glycol ... Preferable examples of the isotonicity agent include ... glycerine ..." (Page 40, lines 4-33). The reference also discloses that a tablet, powder, granule or capsule can be prepared by adding "an excipient, a disintegrating agent, a binder, a lubricant and the like to the compound of the present invention, and subjecting the mixture to compression molding, and where necessary, coating for masking of taste, enteric coating or coating for sustention" (Page 41, lines 12-18). The pharmaceutical preparation can be administered orally (Page 42, lines 26-28) and a sustained release preparation can also be administered (Page 43, lines 8-9). Example 5 discloses the production of 6-(7-hydroxy- 6, 7-dihydro- 5H-pyrrolo [1,2-c] imidazol-7-yl)-N-methyl-2-

naphthamide (Page 58, line 12 to Page 59, line 8).

Tasaka does not expressly teach methacrylic acid copolymers as enteric coating agents and the granules having an average particle diameter of from about 50 to about 2000 μm.

Mazer teaches a system for delivering an active substance with sustained release of the active substance in the intestinal tract (Abstract). The active compound and one or more excipients are formed into a core and coated (Col. 5, lines 42-49). Enteric coating materials of the core particles include methacrylic acid copolymers (Col. 8, lines 15-25). A plasticizer component for the enteric coat component includes triethyl citrate (Col. 8, lines 43-51). An anti-tackiness agent for the enteric coat component comprises talc (Col. 8, lines 52-53). The enteric coating (along with the plasticizer and the anti-tackiness agent) is applied to the core (Col. 10, lines 9-23). The active ingredient granular cores have a particle size range of about 177-420 microns (Col. 10, lines 57-59).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising the compound of formula (I) and an enteric coating, as suggested by Tasaka, combine it with the enteric coating (comprising methacrylic acid copolymers, plasticizer, and anti-tackiness agent) of core particles in the particle size of about 177-420 microns, as taught by Mazer, and produce the instant invention.

One of ordinary skill in the art would do this because methacrylic acid copolymers are known components of enteric coatings, as evidenced by the enteric coating taught by Tasaka (Page 41, lines 12-18) and by the enteric coating of core granules as taught by Mazer (Col. 8, lines 15-25). One of ordinary skill in the art would use the active compound and hydroxypropylcellulose granule of Tasaka and coat these granules with the enteric coating taught by Mazer, with a reasonable expectation of success in producing a controlled release composition with granules of compound of formula (1)-A. Simple substitution of one known element for another to obtain predictable results. See MPEP 2141.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Regarding instant claim 23, the controlled release composition is taught by the composition comprising the compound of formula (I) disclosed by Tasaka (Page 4, lines 1-8 and Page 43, lines 8-9). The core containing (+)-6-(7-hydroxy- 6, 7-dihydro- 5H-pyrrolo [1,2-c] imidazol-7-yl)-N-methyl-2-naphthamide would have been obvious over the compound (+)-6-(7-hydroxy- 6, 7-dihydro- 5H-pyrrolo [1,2-c] imidazol-7-yl)-N-methyl- 2-naphthamide disclosed by Tasaka (Page 6, lines 24-25). The hydrophilic polymer would have been obvious over the hydroxypropylcellulose taught by Tasaka (Page 40, lines 8-10). The enteric coating would have been obvious over the enteric coating taught by Tasaka (Page 41, lines 12-18) and by the enteric coating taught by Mazer (Col. 8, lines 15-25). The methacrylic acid copolymers for enteric coating would have been obvious over the enteric coating materials including methacrylic acid copolymers, as taught by Mazer (Col. 8, lines 15-25). The limitation of talc as a lubricant, and triethyl citrate as the plasticizer would have been obvious over the triethyl citrate plasticizer (Col. 8, lines 43-51), and talc as the anti-tackiness agent (Col. 8, lines 52-53) in the enteric coating, as taught by Mazer. The limitation of the particle diameter of the core granules of from about 50 to about 2000 μm would have been obvious over the granular cores having a particle size range of about 177-420 microns, as taught by Mazer (Col. 10, lines 57-59).

Regarding instant claim 27, the use of the controlled release composition for treating prostate cancer or breast cancer would have been obvious over the pharmaceutical composition used for the treatment of breast cancer or prostate cancer as taught by Tasaka (Page 8, lines 6-14). Moreover, the use of the controlled release composition for "prevention" of prostate cancer or breast cancer is an intended use and has no significance in composition claims.

Applicants respectfully disagree. The amended claim 23 relates to a controlled release composition having the improved sustainability of the effective blood concentration of the active substance. Claim 23 relates to a composition wherein the core is prepared by coating an inert carrier particle with a coating layer comprising (1) Compound A, and (2) hydroxypropylcellulose, and/or low-substituted hydroxypropylcellulose, based on the specification page 63, line 6 to page 64, line 2, Reference Examples 1 and 2, and Examples 5, 6 and 12.

Applicants believe that a conclusion of obviousness cannot be made in view of the U.S. Supreme Court's and the USPTO's current interpretation of obviousness under 35 U.S.C. § 103.

The PTO has issued Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 ("Guidelines") in view of the Supreme Court's recent decision in KSR International Co. v. Teleflex Inc., 550 U.S. __, 82 USPQ2d 1385 (2007), The Guidelines were published in the Fed. Reg., Vol. 72, no. 195, October 10, 2007. As pointed out in the Guidelines, the Supreme Court in KSR reaffirmed the analytical framework for determining obviousness as set forth in Graham v. John Deere Co., 338 U.S. 1, 148 USPQ 459 (1966), and also held that the Federal Circuit's application of its teaching-suggestion-motivation test was too formalistic.

Under Graham, obviousness is a question of law based on underlying factual inquiries that address (1) the scope and content of the prior art, (2) the differences between the claimed invention, and (3) resolving the level of ordinary skill in the pertinent art. Consideration must also be given to secondary factors, such as, for example, evidence of commercial success, long felt but unsolved needs, failure of others, and unexpected results. The Supreme Court stated in KSR that "While the sequence of these questions might be reordered in any particular case, the [Graham] factors continue to define the inquiry that controls." The Guidelines go on to state that "Once the *Graham* factual inquiries are resolved, Office personnel must determine whether the claimed invention would have been obvious to one or ordinary skill in the art."

The Guidelines proceed then to articulate seven independent rationales on which to properly base a rejection under 35 U.S.C. § 103: (1) combining prior art elements according to known methods to yield **predictable results**, (2) substitution of one known element for another to obtain **predictable results**, (3) use of known technique to improve similar devices, methods or products in the same way, i.e., to obtain **predictable results**, (4) applying a known technique to a known device, method or

product ready for improvement to yield **predictable results**, (5) choosing from a finite number of identified, **predictable solutions**, with a reasonable expectation of success, i.e., obvious to try, (6) evidence of design incentives or other market forces sufficient to prompt skilled artisan to vary prior art in a **predictable manner** to result in claimed invention, and (7) evidence of some teaching, suggestion, or motivation in the prior art that would have led the skilled artisan to modify or combine prior art to arrive at claimed invention, i.e., **predictable** modification. All of these tests have the requirement of **predictability**. That is lacking in the present case.

Since the cited references do not disclose or suggest the embodiments wherein a physiologically active substance (Compound A) is contained in a coating layer, we believe that would not have been predictable to one of ordinary skill in the art and, therefore, amended claim 23 overcomes the obviousness rejection under Tasaka et al. in view of Mazer et al.

CONCLUSION

In view of the remarks made herein, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested. Please charge any required fee or credit any overpayment to Deposit Account No. 04-1105.

Dated: July 10, 2009

Respectfully submitted,

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